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K. M. Summers, K. S. Tam, J. W. Halliday, and L. W. Powell

Department of Medicine, University of Queensland, Brisbane

Summary

The frequencies of different HLA-A and -B alleles in 77 Australian patients with hemochromatosis have been compared with frequencies of HLA alleles not associated with hemochromatosis in 63 of their heterozygous relatives and with published population frequencies. As for all other populations reported, an association of HLA-A3 and HLA-B7 with the disease was found. A weak association with HLA-B12 was also detected. No other significant positive or negative associations with HLA alleles were detected. In addition, HLA-A2 and -B12 were in significant linkage disequilibrium in patients but not in controls, which may indicate a new mutation or recent recombination between HLA-A and hemochromatosis either in our patient group or in the founding population. HLA-A1 and -B8 and HLA-A29 and -B12 were in linkage disequilibrium in controls but not in patients, suggesting that this population is not segregating a hemochromatosis allele on either of these haplotypes. Genetic linkage analysis using the program LIPED showed strong linkage in 23/24 families, most of which had additional HLA alleles (other than A3 and B7) associated with hemochromatosis. This provides evidence for a single hemochromatosis locus, possibly with more than one allele.

Introduction

Hemochromatosis is an inherited disease which results in a progressive accumulation of iron in the body, with consequent damage to the liver, heart, and other organs. This is presumably due to mutation in a gene or genes involved in the maintenance of iron homeostasis, although the precise function of this gene is not yet known. The disease is inherited in autosomal recessive fashion, with the disease locus apparently tightly linked to the major histocompatibility complex coding for the human leukocyte antigens (HLA) on chromosome 6 (Cartwright et al. 1979; Simon et al. 1979). Recent population studies (Bassett et al. 1988; Edwards et al. 1988) have shown that the hemochromatosis allele is one of the most common disease alleles in Europeans, with a carrier frequency of about 1/10. Prevalence figures have been summarized by Simon et al. (1988).

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Address for correspondence and reprints: Dr. K. M. Summers, Department of Medicine, University of Queensland, Royal Brisbane Hospital, Herston, Queensland, Australia 4029.

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Population studies have consistently shown strong linkage disequilibrium between the hemochromatosis allele and the HLA-A3 allele (Simon et al. 1987). There is also a smaller disequilibrium between the hemochromatosis gene and HLA-B7 and, in some populations, HLA-B14. The associations with the HLA-B alleles appear to be due to the disequilibrium between these and HLA-A3, and the latter provides the only independent marker of hemochromatosis (Simon et al. 1987). It is not yet clear whether there are other low-frequency alleles at the hemochromatosis locus in linkage disequilibrium or equilibrium with different HLA-A alleles, as has been seen for other common genetic diseases. The prevalence of HLA antigens in hemochromatosis patients in various populations has been presented by Simon et al. (1988).

The present-day Australian population is largely European in origin, with major migration since the 1940s from the United Kingdom, Mediterranean countries, and central Europe (Australian Bureau of Statistics 1986). Considerable founder effect might be expected in the establishment of gene frequencies in this group. Thus the population of Australia represents a unique admixture of genes, different from the major founding

populations (United Kingdom and Southern Europe) and from the admixture found in other colonial groups of European origin. The relatively short time since European settlement (200 years, approximately 7 generations) would have minimized the effects of recent recombination events, and associations between HLA alleles and hemochromatosis might be expected to reflect the relationships in the founding populations. We therefore considered that a study of HLA associations with hemochromatosis in Australian families might help show (*a*) whether there is one or more locus coding for genes involved in iron homeostasis which, when mutated, cause hemochromatosis and (*b*) whether there may be more than one such mutant allele at this locus (loci).

Subjects and Methods

Diagnosis of hemochromatosis was based on evidence of increased mobilizable parenchymal iron stores as detected by one or more of the following indications (Bassett et al. 1986): stainable iron greater than grade 2 in the liver, hepatic iron concentration >60 μmol/g dry weight, hepatic iron index (hepatic iron concentration/age) >2 (Bassett et al. 1986), removal of >2.5 g iron by repeated phlebotomy, and >2.2 mg iron excreted in the 24 h following administration of 0.5 g desferrioxamine (Balcerzak et al. 1968). In all cases, other known causes of iron overload (such as iron-loading anemias) were excluded (Powell et al. 1980).

The study group included 77 hemochromatosis patients, from 52 families of European origin, who had 129 independent HLA-A and -B alleles. Where more than one family member was affected, each independent HLA haplotype associated with hemochromatosis was counted once only. Family studies showed that at least 16 homozygous-heterozygous matings and two possible homozygous-homozygous matings had occurred. Ninety-eight of the HLA-A and -B alleles in patients could be assigned to definite haplotypes on the basis of pedigree information; the remainder could not be unequivocally assigned.

HLA alleles not shared with an affected family member in heterozygous siblings, offspring, or parents of a patient were considered not to be associated with hemochromatosis. Seventy-four obligate heterozygotes yielded 63 independent HLA-A and -B alleles. All heterozygous individuals were clinically asymptomatic, and, where tested, none of the five indicators of disease was positive, although some of these individuals had raised serum ferritin or transferrin saturations. This control group differs from those in previous studies in that it includes no hemochromatosis-associated HLA alleles. Results were also compared with those for a blood-bank control group (Baur and Danilovs 1980), among whom approximately 10% will be carriers of one hemochromatosis allele and among whom 1/400 will be affected.

HLA typing was performed by standard methods by the Immunology Laboratory at Princess Alexandra Hospital, Brisbane, or by the Sydney Blood Transfusion Service. Typing began in the 1970s, and certain antigen subtypes were not recognized for some subjects. Thus Bw44 was scored as B12, Bw51 as B5, Bw57 as B17, Bw60 as Bw40, and Bw62 as B15 in the combined results. The subtypes were retained in the analysis of families where appropriate.

Allele frequencies in the groups were compared using the χ^2 contingency test without Yates's correction, since the numbers are sufficiently large (Sokal and Rohlf 1969, p. 590). To allow for random associations detected because of the large number of comparisons being made, probabilities were multiplied by the number of comparisons, as indicated in the Results section. Linkage disequilibrium between two loci was assessed using the association Δ_r, calculated by the formula quoted by Baur and Danilovs (1980):

$$\Delta_r = \frac{\text{(haplotype frequency)} - \text{(product of allele frequencies)}}{\text{(frequency of locus 1 allele)} \cdot \text{(1 − frequency of locus 2 allele)}} .$$

The significance of this association was determined using the χ^2 contingency test. Linkage analysis was carried out using the program LIPED supplied by Dr. Jurg Ott, Columbia University, New York. For linkage analysis, HLA haplotypes were coded according to the suggestion of Ott (1978) to avoid problems due to large numbers of different alleles and genotypes.

Results

HLA Alleles Associated with Hemochromatosis

In this Australian population of families with hemochromatosis, the HLA-A3 antigen was detected in 48/77 (62%) of patients, and 13 of these were apparently homozygous for the allele coding for this antigen, on the basis of HLA typing and pedigree analysis. The HLA-B7 antigen was found in 38/77 (49%) patients, with eight apparently homozygous. Of these, five patients were typed as expressing only the A3 and B7 an-

tigens (probable double homozygotes). A3 is found in 24% and B7 in 21% of the published controls (Baur and Danilovs 1980).

Because extensive family data allowed us to distinguish between homozygosity and null alleles at the HLA-A and -B loci, we were able to determine HLA allele frequencies for our patient and heterozygous groups. The 77 patients yielded 129 independent chromosomes carrying a hemochromatosis gene. Table 1 gives the frequencies of HLA-A and -B alleles that are found on these chromosomes and that therefore are associated with hemochromatosis in this population. Table 1 also shows allele frequencies for the 63 nonhemochromatosis haplotypes in heterozygous subjects with no evidence of iron overload. These are compared with allele frequencies in the published Australian Caucasian population. The range of HLA-A and -B alleles was similar in hemochromatosis and nonhemochromatosis haplotypes, with only three alleles uniquely present in one group or the other.

Frequencies of all HLA-A and -B alleles in hemochromatosis and control groups were compared using the χ^2 contingency test. Although a number of significant results were initially seen, most of these could

Table 1

HLA Alleles in Families with Hemochromatosis

	Linked to Hemochromatosis			Not Linked to Hemochromatosis			Baur and Danilovs (1980) Frequencies	
Allele	N	Uncorrected Frequency (%)	Corrected Frequency[a] (%)	N	Uncorrected Frequency (%)	Corrected Frequency[a] (%)	Uncorrected Frequency (%)	Corrected Frequency[a] (%)
A1	18	13.9	23.4	10	15.8	19.2	18.6	21.4
A2	31	24.0	40.1	13	20.6	25.0	23.8	27.4
A3	53	41.1	...	11	17.5	...	13.1	...
A11	5	3.8	6.6	7	11.1	13.5	6.6	7.6
Aw23	0	0	0	2	3.2	3.8	2.4	2.8
Aw24	8	6.2	10.5	9	14.3	17.3	7.2	8.3
A25	1	.8	1.3	1	1.6	1.9	3.6	4.1
A26	2	1.6	2.6	1	1.6	1.9	3.0	3.4
A28	4	3.1	5.3	3	4.8	5.6	5.1	5.9
A29	2	1.6	2.6	5	7.9	9.6	4.5	5.2
Aw30/w31	2	1.6	2.6	0	0	0	3.9	4.5
Aw32	3	2.3	3.9	1	1.6	1.9	4.2	4.8
Other	...	...	...	...	...	...	4.4	5.1
B5	3	2.3	3.3	1	1.6	1.9	4.2	4.7
B7	40	31.0	...	9	14.3	...	11.1	...
B8	13	10.1	14.6	6	9.5	11.1	12.8	14.4
B12	27	20.9	30.3	12	19.0	22.2	13.3	15.0
B13	0	0	0	2	3.2	3.7	2.4	2.7
B14	6	4.7	6.7	3	4.8	5.6	6.0	6.7
B15	4	3.1	4.5	3	4.8	5.6	6.3	7.1
B17	9	7.0	10.1	6	9.5	11.1	4.8	5.4
B18	1	0.8	1.1	0	0	0	3.6	4.0
Bw22	1	0.8	1.1	1	1.6	1.9	3.6	4.0
B27	3	2.3	3.4	8	12.7	14.8	5.1	5.7
Bw35	11	8.5	12.4	6	9.5	11.1	6.3	7.1
B37	2	1.6	2.2	0	0	0	1.5	1.7
Bw38	2	1.6	2.2	0	0	0	1.5	1.7
Bw39	0	0	0	1	1.6	1.9	0.9	1.0
Bw40	6	4.7	6.7	4	6.3	7.4	9.1	10.2
Bw41	1	0.8	1.1	0	0	0	0.9	1.0
Bw49	0	0	0	1	1.6	1.9	1.5	1.7
Other	...	...	...	...	...	...	5.9	6.6

[a] With the effects of A3 or B7 removed.

be disregarded when allowance was made for the large number of comparisons. This was done by multiplying the probability of the χ^2 result by the number of comparisons. Three results remained significant when this adjusted probability was examined. HLA-A3 and -B7 were higher in hemochromatosis patients than in the published control group (χ^2 = 44.79 and 27.15, respectively; $P_{adjusted} < .01$). HLA-A3 was also higher in patients than in the heterozygous control group (χ^2 = 10.63; $P_{adjusted} < .05$), but the increase in HLA-B7 was not statistically significant (χ^2 = 6.22).

Simon et al. (1987) have shown that the increased space taken by the A3 and B7 alleles can have the effect of artificially decreasing the frequencies of other alleles, which may mask frequency differences. Corrected frequencies were calculated according to the procedure outlined by Simon et al. (1987) to examine this possibility, and these frequencies are also shown in table 1. The corrected frequency of HLA-B12 was apparently increased compared with that in the published control group (although it was not increased compared with that in the heterozygous control group). This difference remained significant when the probability was adjusted for the number of comparisons (χ^2 = 10.72; $P_{adjusted} < .05$). There was no significant effect on the corrected frequencies of HLA-A1, -A11, -B14, or -Bw35.

Where pedigree analysis allowed the HLA-A and -B alleles to be assigned to haplotypes, 42 different haplotypes were seen in 98 independent chromosomes in patients (table 2). Twenty-two (22%) of these chromosomes carried the A3, B7 haplotype. There were 37 different haplotypes in the 63 nonhemochromatosis

Table 2

HLA Haplotypes in Families with Hemochromatosis

	Linked to Hemochromatosis			Not Linked to Hemochromatosis		
Haplotpye	*N*	Uncorrected Frequency (%)	Corrected Frequency[a] (%)	*N*	Uncorrected Frequency (%)	Corrected Frequency[a] (%)
A3,B7	22	22.4	. . .	5	7.9	. . .
A2,B12	9	9.2	11.8	3	4.8	5.2
A3,Bw35	5	5.1	6.6	1	1.6	1.7
A1,B17	4	4.1	5.3	4	6.3	6.9
A3,B14	4	4.1	5.3	2	3.2	3.4
A3,B12	4	4.1	5.3	0	0	0
A1,B8	3	3.1	3.9	5	7.9	8.6
A2,B8	3	3.0	3.9	0	0	0
A2,B15	2	2.0	2.6	3	4.8	5.2
Aw24,B12	2	2.0	2.6	2	3.2	3.4
Aw24,Bw35	2	2.0	2.6	1	1.6	1.7
A1,B7	2	2.0	2.6	1	1.6	1.7
A1,B37	2	2.0	2.6	0	0	0
A1,B40	2	2.0	2.6	0	0	0
A2,B7	2	2.0	2.6	0	0	0
A3,B5	2	2.0	2.6	0	0	0
A11,B27	2	2.0	2.6	0	0	0
A28,B12	2	2.0	2.6	0	0	0
A29,B12	1	1.0	1.3	5	7.9	8.6
A3,B27	1	1.0	1.3	2	3.2	3.4
Aw24,B27	1	1.0	1.3	2	3.2	3.4
A2,B40	1	1.0	1.3	1	1.6	1.7
A11,Bw35	1	1.0	1.3	1	1.6	1.7
Aw24,B17	1	1.0	1.3	1	1.6	1.7
A2,B27	0	0	0	2	3.2	3.4
A11,B13	0	0	0	2	3.2	3.4
Aw24,B27	0	0	0	2	3.2	3.4
Others[b]	20	20.4	23.7	18	28.6	31.0

[a] With A3,B7 removed.

[b] Haplotypes that appeared once in only one category.

chromosomes. Five (8%) of these 63 were A3,B7. This difference in frequency of A3,B7 produced a χ^2 value of 5.79, which is not significant when allowance is made for the large number of comparisons ($P_{adjusted} \sim .4$). No other haplotype was different in patients compared with controls when similarly adjusted probabilities were used. As seen in table 3, A3 and B7 were in linkage disequilibrium in patients and controls. It is interesting that A2 and B12 were in disequilibrium in patients but not in controls, while A1 and B8, A3 and B14, and A29 and B12 were in disequilibrium in controls but not in patients. A1 and B17 were in negative equilibrium in patients but in positive disequilibrium in controls, and A3 and B12 were in negative disequilibrium in patients but in linkage equilibrium in controls.

Linkage of HLA to Hemochromatosis

Linkage between the MHC and hemochromatosis was analyzed in 24 families in whom complete HLA typing of all key members was available or could be deduced so that HLA type could be recoded by the method of Ott (1978). The results of this analysis are shown in table 4. All except one family showed positive linkage to HLA. Positive linkage was detected in four families (8, 13, 21, and 23) in whom neither A3 nor B7 was found in any affected individual, in three families (7, 10, and 20) in whom A3 but not B7 was found, and in one family (24) with B7 but not A3. The total LOD score for these families was 18.8 at a recombination fraction in males and females of 2.1% (95% confidence interval 0.4%–6%). When the female recombination fraction was set at the twice male recombination fraction (Lalouel et al. 1985), a maximum LOD score of 18.9 was achieved at a male recombination fraction of 1.4% (95% confidence interval 0.3%–3.9%).

Three obligate recombinants were found, in families 14, 19, and 23. In family 19, a small nuclear family, this resulted in negative linkage; but families 14 and 23 are large, multigeneration, extended pedigrees, and positive linkage was detected. Two further recombinants were found in the 28 families that could not be included in the linkage analysis. These recombinants are discussed further by Powell et al. (1988).

An interesting result was obtained with family 18, which consists of two affected brothers, who share no haplotype, and the affected offspring of one of these, who clearly show HLA linkage. A maximum LOD score of 0.60 at a recombination fraction of zero was found. The difference in the HLA types of the affected brothers may result from a homozygote-homozygote mating or from a homozygote-heterozygote mating with one recombination, although the possibility of nonpaternity cannot be eliminated. This family has been discussed in detail by Powell et al. (1988).

Table 3

Linkage Disequilibrium for Frequent HLA Haplotypes in Families with Hemochromatosis

	Linked to Hemochromatosis			Not Linked to Hemochromatosis		
Haplotype	N	Δ_r	χ^2_1	N	Δ_r	χ^2_1
A3,B7	22	.30	19.2***	5	.38	10.6**
A2,B12	9	.26	7.1**	3	.08	.4
A3,Bw35	5	.03	.6	1	.03	0
A1,B17	4	−.56	9.1**	4	.31	12.8***
A3,B14	4	.05	2.8	2	.13	5.29*
A3,B12	4	−.13	5.82*	0	.20	.26
A1,B8	3	.13	2.25	5	.44	22.6***
A29,B12	1	.03	1.1	5	.42	25.8***

*$.01 < P < .05$.
**$.001 < P < .01$.
***$P < .001$.

Discussion

In this Australian population, as in all other populations of predominantly European origin that have been studied, hemochromatosis is significantly associated with HLA-A3 and -B7. While associations with A1, A11, B14, Bw35, and Bw47 have been reported previously, none of these antigens was found in increased frequency in our population, even when frequencies were corrected for effects of high values for A3 and B7. The corrected frequencies of A2 and B12 in patients were marginally increased over the frequency in heterozygous controls and over the corrected published frequencies, with the result for B12 compared with that for published controls being significant at $P_{adjusted} < .05$. No HLA-A or -B allele was significantly depleted when frequencies were corrected for the high frequency of A3 or B7. An alternative control group from unpublished data of T. J. Doran and H. V. Bashir (New South Wales Blood Transfusion Service, Sydney) gave very similar results, except that the increase in the corrected frequency of B12 was no longer significant ($\chi^2 = 4.55$).

Differences between the nonhemochromatosis control group presented here and the published frequencies are probably attributable to the small size of our group ($N = 63$). It might be expected that there would be an increase in the hemochromatosis-associated al-

Table 4

Linkage Between HLA and Hemochromatosis

Family	No. Affected	No. Not Affected[a]	θ_{max}[b]	LOD at θ_{max}	HLA Alleles Linked to Hemochromatosis	
					HLA-A	HLA-B
1	4	5	0	1.81	3,11	7,27,w51
2	1	13	0	1.37	3	7,w51
3	1	3	0	.13	3	7,18
4	1	3	0	.13	3	7
5	4	5 (2)	0	1.29	2,3,w24	7,8,12
6	3	4	0	1.20	2,3	7,12
7	2	2 (2)	0	.84	3,w30/w31	14,w35
8	3	1 (1)	0	.60	2,w24,28	w35,w44,w57
9	3	2 (2)	0	1.40	3	7,w35
10	2	6	0	1.10	2,3	14,w44
11	1	6 (1)	0	.62	3	7,w35
12	1	3 (1)	0	.26	3	7
13	3	5 (1)	0	.98	2,w24	15,17
14	5	6 (1)	.10	.78	1,3,w32	7,8,w35,w44,w60
15	7	7 (2)	0	2.29	1,2,3,	7,8,12,w35
16	2	6	0	1.10	3	1,40
17	1	3 (1)	0	.24	3,28	,7,12
18	4	2	0	.60	3,29,w32	7,8,12,w22
19	1	3	.50	0	1,3	7,w44
20	2	5 (2)	0	.80	2,3	14,w44
21	2	2 (1)	0	.70	1,28	w44,w57
22	2	2 (2)	0	1.38	3,w24	7,17
23	4	11	.08	1.02	2,11	8,12,27
24	2	4	0	.85	2,w24	7,w44

[a] Numbers in parentheses are numbers of individuals who were not available for clinical assessment so that their hemochromatosis phenotype is unknown (although HLA types could be deduced from other family members).

[b] Recombination fraction that gives the maximum LOD score.

leles in the published frequencies compared with our nonhemochromatosis controls (owing to the approximately 1/10 carrier frequency for the hemochromatosis allele). However, there is no evidence for this phenomenon, perhaps again owing to the small size of our heterozygous control population. Similarities between our patient and heterozygote groups would indicate that the population of hemochromatosis families is less heterogeneous with respect to HLA type than is the general population from which the published frequencies are drawn.

We also looked at haplotypic associations with hemochromatosis and at patterns of linkage disequilibrium and equilibrium in patients and controls. As in other studies, we found that the only positive association was with the HLA-A3,B7 haplotype, but in our group the significance of the association disappeared when the probability was corrected for the number of comparisons made. A larger sample size would be necessary to demonstrate the magnitude of the association in our population. HLA-A3,Bw35 is the most frequent marker of hemochromatosis in northern Italy (Zacchi et al. 1982; Piperno et al. 1986) and shows marginally increased frequency in our patient population, presumably reflecting the major migration from Italy to Australia in the past few decades (Castles 1988). The A3,B14 haplotype occurs at similar frequencies in patients and controls, showing that this association, reported from Brittany in France (Simon et al. 1988), is not present in our patients. The haplotype HLA-A1,B8 is not increased. This association has been reported in Sweden (Ritter et al. 1984). Scandinavian groups have made only a small contribution to the population in Australia. Since the HLA-A1 and -B8 alleles are in strong linkage disequilibrium in our controls but not in our patients, it appears that a hemochromatosis allele associated with

this haplotype has not been introduced into Australia. In addition, the association of hemochromatosis with the HLA-A1,B8 haplotype has not been found in Denmark (Milman et al. 1988), and it seems likely that it represents a recent recombination or mutation event which has not yet diffused beyond the localized region.

The strong linkage disequilibrium between A2 and B12 in the patients may indicate that this population is segregating a second hemochromatosis allele due to mutation on a chromosome carrying this haplotype. This result could also have been caused by a single recombination event between HLA-A and the hemochromatosis locus that introduced the hemochromatosis allele on to an HLA-A2,B12 chromosome. A2 and B12 are not in linkage disequilibrium in the control group. The linkage of a hemochromatosis allele to the A2,B12 haplotype probably occurred recently, as the frequency of this chromosome has not yet increased significantly in the patient group.

Analysis of linkage of hemochromatosis to the antigens of the MHC showed positive genetic linkage in 23/24 families. Hemochromatosis genes linked to HLA-A3 and those linked to other HLA-A types were clearly allelic to each other, providing evidence for a single hemochromatosis locus about 2 cM from the MHC. Previous reports have given equivalent or slightly lower recombination frequencies. Coding haplotypes as single alleles tends to inflate the recombination fraction if there are recombinants within the HLA region, but this is unlikely to have had a large effect in our study. Parents are fully informative in two of the three families with obligate recombinants, and there is no evidence for a recombination between HLA-A and -B. In the third family, family 23, one parent was homozygous for A2 and B12, and the affected and unaffected haplotypes could only be distinguished by DR type. The apparent recombination could have occurred anywhere between the HLA-DR locus and the hemochromatosis gene. The recombination fraction is increased because of the results for family 19. In this four-member nuclear family, an affected female (age 18 years at diagnosis) has an HLA-identical unaffected brother (age 24 years at most recent examination). As discussed elsewhere (Powell et al. 1988), it is possible that this male will develop the disease and that use of an age-dependent penetrance would reduce the impact of this family on the result. Clearly, therefore, in at least 23 of these 24 families hemochromatosis is HLA linked and disease genes carried on HLA-A3,B7 chromosomes are allelic to those on chromosomes with other HLA haplotypes. This provides strong evidence that a single genetic locus is involved in the majority of (probably all) cases of familial hemochromatosis in Australia, although our results suggest that there could be other disease-causing alleles at this locus.

Simon et al. (1988) have suggested that a single, ancient mutation of a gene involved in iron homeostasis resulted in the present-day hemochromatosis allele. This mutation is thought to have occurred on a chromosome carrying HLA-A3 and -B7. Over the years, recombination events between the HLA-A and -B loci have presumably led to the observed associations with other HLA-B alleles on haplotypes carrying HLA-A3, and recombinations between HLA-A and the hemochromatosis locus have produced associations with other HLA-A alleles and haplotypes. This original mutation should be progressing toward equilibrium with the HLA alleles, although an association with HLA-A3 still remains in all populations studied, including the present group, either because there has been insufficient time to reach equilibrium or because the association confers a selective advantage (Kushner et al. 1988). The recent mutation or recombination event that has placed a hemochromatosis allele on an HLA-A2,B12 chromosome would have occurred in a population that has made a major contribution to the present-day Australian gene pool but that has contributed less to present-day European and other colonial populations. Price (1988) has shown that the derivation of the present-day Australian population is approximately 44% English, 17% Irish, and 12% Scottish, with other European groups contributing less than 4%. An origin in England or (in view of the family names of many of our patients) Ireland thus seems likely for the linkage disequilibrium of HLA-A2 and -B12 in this group of hemochromatosis patients. Conversely, HLA-A1 and -B8 are in tight linkage disequilibrium in controls but not in patients, a finding reflecting the low level of migration from Scandinavia (where an association of hemochromatosis with these HLA alleles exists) to Australia.

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